HHS Public Access

Author manuscript

J Pediatric Infect Dis Soc. Author manuscript; available in PMC 2019 April 13.

Clinical characteristics of hospitalized infants with laboratory-confirmed pertussis in Guatemala

Varun K. Phadke[1], **John P. McCracken**[2], **Jennifer L. Kriss**[3], **Maria R. Lopez**[2], **Kim A. Lindblade**[4], **Joe P. Bryan**[4,5], **Miguel E. Garcia**[6], **Carlos E. Funes**[7], and **Saad B. Omer**[3,8,9]

[1]Division of Infectious Diseases, School of Medicine, Emory University, Atlanta, GA USA

[2]Center for Health Studies, Universidad del Valle de Guatemala, Guatemala City, Guatemala

[3]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA USA

[4]Division of Global Health Protection, Centers for Disease Control and Prevention, Central American Regional Office, Guatemala City, Guatemala

[5]Division of Global Health Protection, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, GA, USA

[6]Department of Pediatrics, Hospital Nacional de Cuilapa, Santa Rosa, Guatemala

[7]Department of Pediatrics, Hospital Regional de Occidente, Quetzaltenango, Guatemala

[8]Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA

[9]Emory Vaccine Center, Emory University, Atlanta, GA, USA

Abstract

Background—Pertussis is an important cause of hospitalization and death in infants too young to be vaccinated (aged <2 months). Limited data on infant pertussis have been reported from Central America. The aim of this study was to characterize acute respiratory illnesses (ARI) attributable to *Bordetella pertussis* among infants enrolled in an ongoing surveillance study in Guatemala.

Methods—As part of a population-based surveillance study in Guatemala, infants aged <2 months presenting with ARI who required hospitalization were enrolled and nasopharyngeal and oropharyngeal swab specimens were obtained. For this study these specimens were tested for *B. pertussis* using real-time polymerase chain reaction (PCR).

Results—Among 301 infants hospitalized with ARI, we found 11 with pertussis confirmed by PCR (pertussis-positive infants). Compared to pertussis-negative infants, pertussis-positive infants had a higher mean admission white blood cell count (20,900 vs. 12,579 cells/μl, p=0.024), absolute lymphocyte count (11,517 vs. 5,591 cells/μl, p<0.001), rate of admission to the intensive

Corresponding author: Varun K. Phadke, MD (vphadke@emory.edu), 49 Jesse Hill Jr. Drive, Atlanta, GA, USA 30303, Phone: 716-430-3043 / Fax: 404-880-9305.
Alternate corresponding author: Saad B. Omer MBBS MPH PhD (somer@emory.edu), 1518 Clifton Road NE, Room 7017 (CNR Building), Atlanta, GA, USA 30322, Phone: 404-727-9814 / Fax: 404-727-4590

care unit (ICU) (64 vs. 35%, p=0.054), and case fatality rate (18 vs. 3%, p=0.014). Ten of the 11 pertussis-positive infants had cough at presentation, and the majority (80%) of these had a cough duration of <7 days and only one had a cough duration >14 days. Fever (temperature ≥ 38°C) was documented in nearly half (45%) of pertussis-positive infants (range, 38.0–38.4°C).

Conclusions—In this study of infants <2 months of age hospitalized with ARI in Guatemala, pertussis-positive infants had a high rate of ICU admission, and a higher case fatality rate than pertussis-negative infants.

Keywords

Pertussis; Guatemala; infants; case definitions

Introduction

Pertussis remains a significant cause of morbidity and mortality in young children, particularly infants <2 months of age who are too young to be vaccinated [1–3]. Interventions to prevent pertussis in this age group – including immunization of pregnant and postpartum women, close contacts of young infants, and health care workers – have been introduced in some countries [4–8]. Although maternal immunization with pertussis-containing vaccines is one of the most effective strategies, it is not routine in many developing countries. To support introduction of routine maternal pertussis immunization in low- and low-middle income countries, high-quality data on infant pertussis epidemiology are needed [9]. In Latin America, surveillance studies of infant pertussis have been reported from Mexico [10], Costa Rica [11], Panama [12], Argentina [13], and Brazil [14]; however, similar data from other countries in the region, including many in Central America, are lacking [15].

Many Latin American countries conduct pertussis surveillance using the World Health Organization (WHO) or the US Council of State and Territorial Epidemiologists (CSTE) case definitions for pertussis [16, 17] (Table 1). However, during recent pertussis epidemics in the United States (US) and the United Kingdom, observational studies found that the clinical presentation of laboratory-confirmed pertussis in young infants was often atypical when viewed in the context of these published case definitions [18–20]. Given these observations, a significant proportion of infant pertussis may be unrecognized and the burden underestimated in low and low-middle income countries.

To begin to address this issue, we used data from a surveillance study of acute respiratory illness (ARI) hospitalizations in Guatemala [21], where maternal pertussis vaccination is not routine, and identified pertussis among hospitalized infants aged <2 months by testing nasopharyngeal and/or oropharyngeal specimens using a real-time polymerase chain reaction (rt-PCR) assay for *Bordetella pertussis*. Using data from parental interview and medical charts, we characterized the epidemiologic and clinical characteristics of pertussis in this vulnerable population.

Methods

Surveillance and case ascertainment

As part of a collaboration between the Guatemalan Ministry of Health, the US Centers for Disease Control and Prevention (CDC) and the Universidad del Valle de Guatemala (UVG), surveillance of hospitalized ARI is conducted in two departments of Guatemala (Santa Rosa and Quetzaltenango). Full details of these surveillance sites have been described in a previous report [21]. ARI in children aged <2 years was defined as: (1) at least one sign of acute infection (either temperature ≥ 38°C or ≤ 35.5°C, or an abnormal white blood cell count (WBC) [defined as <5550 or >11000 cells per microliter], or an abnormal differential), and (2) at least one respiratory sign/symptom (either rapid breathing, cough, sputum production, pleuritic chest pain, hemoptysis, dyspnea, or sore throat; apnea was not included) or inability to feed, noisy breathing, or nasal flaring. After February 2011, we also included children aged <5 years who satisfied the WHO Integrated Management of Childhood Illness (IMCI) clinical criteria for empiric therapy of suspected pneumonia (or severe pneumonia) in those aged 2 months to 5 years [22]. These criteria require any one of the following: cough with rapid breathing (≥ 50 breaths per minute for children aged 2 months to 12 months, and ≥ 40 breaths per minute for children aged 12 months to 5 years), chest in-drawing, stridor or any general danger sign (defined as the inability to drink or breastfeed; persistent vomiting; loss of consciousness; lethargy; or convulsions; apnea again not included) [22]. For this study, we focus on ARI hospitalizations in infants aged <2 months from 2009 to 2012.

Data collection

Clinical and laboratory data for enrolled infants were collected by surveillance nurses from parental interviews and medical charts. Nasopharyngeal (NP) and oropharyngeal (OP) swabs were collected in line with best practice guidance from CDC. Study nurses donned masks, goggles, and gloves prior to NP/OP swab sampling, and only opened the transport media container around the time of specimen collection, and swabs were collected from hospitalized infants in locations remote from those used for pertussis vaccine storage or preparation. After collection, NP/OP swabs were placed in viral transport media (NP and OP swabs combined in one vial), and transported to the laboratory at the Universidad del Valle de Guatemala for rt-PCR testing.

For this study, these specimens were tested for *B. pertussis* by rt-PCR using reagents and protocols described by Tatti et al [23]. All rt-PCR assays were conducted alongside a positive and negative control for *B. pertussis*. During the extraction process, negative controls were included to ensure that there was no cross-contamination between samples. Furthermore, an internal positive control (*rnaseP*) was used to verify nasopharyngeal sample quality (the cycle threshold (Ct) values for *rnaseP* for all the specimens in this study were <40). Specimens that tested positive for both insertion sequence IS*481* (cycle threshold (Ct) value <40) and pertussis toxin subunit S1 *ptxS1* (Ct value <40) by PCR were considered positive for *B. pertussis*. Specimens that tested positive only for IS*481* (Ct value <35) and negative for *ptxS1* were considered positive for *Bordetella* species; those with Ct values for IS*481* that were ≥35 and <40 were considered indeterminate. Finally, specimens that tested

positive only for *ptxS1* (Ct value <40) and negative for IS*481* were considered positive for *B. parapertussis*. We did not perform additional PCR testing using *B. holmesii* specific targets.

Data analysis

We conducted descriptive analyses of baseline characteristics, clinical features, and outcomes in relation to pertussis PCR test results. We used chi-square tests and t-tests to assess differences in proportions and means between the comparison groups. Differences were considered statistically significant at $p<0.05$. SAS version 9.3 was used for all analyses (SAS Institute, Cary, NC).

Human subjects

The protocol for the overall surveillance study was approved by the ethics review committees of the Universidad del Valle in Guatemala (Guatemala City, Guatemala), the US CDC (Atlanta, GA USA), and the Guatemala Ministry of Public Health and Social Welfare (Guatemala City, Guatemala). This study was exempted from additional review. Eligible infants that were hospitalized with ARI were enrolled after parents or guardians provided written informed consent [21].

Results

During the surveillance period, there were 355 infants aged <2 months who were hospitalized with ARI in Santa Rosa and Quetzaltenango. Of these, 323 infants (91%) were enrolled into the overall surveillance study, and a NP/OP swab specimen was obtained from 319 (90%). A total of 301 aliquots (94% of the NP/OP specimens collected) were available for rt-PCR testing for *B. pertussis*, and only data from these subjects were used in subsequent analyses. Of these 301 subjects, 186 (62%) were enrolled prior to February 2011 based on the ARI case definition (although 160 of these also met the WHO IMCI clinical criteria). After February 2011, 22 subjects (7%) were enrolled based on the ARI definition alone, 23 (8%) were enrolled based on the WHO IMCI criteria alone, and 70 (23%) met both the ARI and WHO IMCI case definitions for enrollment. Out of the 301 infants with a NP/OP swab specimen available for testing, 11 (3.7%) tested positive for *B. pertussis* (hereafter referred to as the pertussis-positive infants) and one (0.3%) tested positive for *B. parapertussis*.

Baseline characteristics

Seven (64%) of the 11 pertussis-positive infants were from the Santa Rosa site and four (36%) were from the Quetzaltenango site. The mean age of the pertussis-positive infants was 36.8 days (SD 11 days, range 22–52 days). In this group, seven (37%) were male, ten (91%) were breastfed, and three (27%) had been born preterm (reported as a dichotomous variable by the parents; specific gestational age data were not available for this analysis). No significant differences were observed between pertussis-positive and pertussis-negative infants in the baseline characteristics of age, sex, department of residence, breast-feeding status, and preterm birth (Table 2).

Outcomes and clinical features

The clinical course and outcomes are shown in Table 3. There were two (18%) deaths among the 11 pertussis-positive infants, compared to ten (3%) among the 290 pertussis-negative infants (p=0.014). One of the pertussis-positive infants who died was born preterm. A greater proportion of the pertussis-positive infants required admission to the intensive care unit (ICU) than the pertussis-negative infants (64% vs. 35%), though this difference was not statistically significant (p=0.054). Among infants admitted to the ICU, the pertussis-positive and pertussis-negative infants had similar mean lengths of stay (5.9 vs. 5.3 days respectively, p=0.712). Three (27%) of the 11 pertussis-positive infants had been diagnosed with pertussis clinically by a treating physician, compared to four (1%) of the 290 pertussis-negative infants (p<0.001).

Five (45%) of the 11 pertussis-positive infants had a fever (temperature ≥ 38°C within the first 24 hours of hospitalization), with temperatures ranging from 38.0 to 38.4°C; this was not significantly different from the proportion (178, or 61%) of the 290 pertussis-negative infants who had fever. Seven (64%) of the 11 pertussis-positive infants met clinical criteria for empiric treatment for presumed pneumonia, defined according to the WHO IMCI handbook for children aged 2 months to 5 years [22], compared to 252 (87%) of the 290 pertussis-negative infants (p=0.024). A higher proportion of the 11 pertussis-positive infants had seizures compared to the 290 pertussis-negative infants (18 vs. 5%) (further clinical details on the seizures were not captured), but this difference was not statistically significant (p=0.067).

Hematologic parameters were available from ten (91%) of the 11 pertussis-positive infants and 218 (75%) of the 290 pertussis-negative infants. The mean admission WBC among the 11 pertussis-positive infants (20,900 cells per microliter, range 8,900–36,100) was greater than for the 290 pertussis-negative infants (12,579 cells per microliter, range 3,000–71,900; p=0.024). Similarly, the mean admission absolute lymphocyte count (ALC) was significantly higher in the 11 pertussis-positive infants (11,517 cells per microliter, range 3,391–18,880) compared with the 290 pertussis-negative infants (5,591 cells per microliter, range 132–22,792; p<0.001). The mean admission WBC and ALC were not significantly higher among the pertussis-positive infants who died compared to those that survived.

Detailed clinical information for the 11 pertussis-positive infants collected at the time of presentation is summarized in Table 4. In terms of presenting symptoms, ten (91%) of the 11 pertussis-positive infants had a cough at the time of presentation, and their mean cough duration prior to admission (defined as the duration of cough prior to hospitalization) was 5.3 days (SD 4.3 days, range 1–15 days). The cough duration prior to hospitalization did not differ between the pertussis-positive and pertussis-negative infants (p=0.354). Of the 10 pertussis-positive infants who had a cough at the time of hospitalization, eight (80%) had been coughing for <7 days, and of the remaining two, only one had been coughing for longer than 14 days. In the main surveillance study, more specific details about the nature of the cough illness, including the presence of paroxysmal cough, whoop, or post-tussive emesis, were not collected from infants who had been coughing for ≤7 days at the time of hospitalization. However, in the two pertussis-positive infants who had been coughing for >7 days, only one had whoop, and neither infant had had paroxysmal cough or post-tussive

emesis. In terms of laboratory findings, hematologic data were available from 10 of the 11 pertussis-positive infants, and of these, five (50%) had an admission WBC greater than 20,000 cells per microliter, and seven (70%) had an admission ALC greater than 10,000 cells per microliter.

All infants had previously undergone testing for respiratory syncytial virus (RSV) and influenza A and B as part of the overall ARI surveillance study – among the 11 pertussis-positive infants, two (18%) had co-infection with RSV and none had concomitant influenza. Three (33%) of nine pertussis-positive infants for whom chest X-ray (CXR) interpretation was available had findings of alveolar consolidation, though in one patient, the CXR was not obtained until hospital day nine. Two (22%) additional pertussis-positive infants had infiltrates without definite consolidation, as defined by the WHO radiological criteria for pneumonia [24].

Discussion

This is the first report of the epidemiologic and clinical characteristics of laboratory-confirmed infant pertussis from Guatemala. Using rt-PCR we identified 11 infants with laboratory-confirmed pertussis among a group of 301 infants <2 months of age hospitalized with ARI in two departments of Guatemala. A high proportion of these pertussis-positive infants had severe disease with complications, including seven (64%) that required ICU admission and two (18%) deaths. These rates of complications are similar to those reported for hospitalized infants with pertussis from a variety of geographic regions [11, 19, 20, 25–28], including several countries in Latin America, such as Mexico [10], Costa Rica [11], Panama [12], Argentina [13], and Brazil [14]. Notably, these same countries have experienced a resurgence of pertussis in recent years, with a number of infant hospitalizations and deaths, and have since introduced routine maternal pertussis immunization into their national vaccination programs [17].

Based on our clinical data, only one of the pertussis-positive infants met the clinical criteria specified by the WHO case definition for pertussis, which requires a cough duration of ≥14 days at the time of presentation [29]. However, two other pertussis-positive infants who did not meet the WHO clinical criteria were diagnosed with pertussis by a physician. In our study, the majority (80%) of pertussis-positive infants actually had a cough duration of ≤7 days at the time of hospitalization. This finding is similar to what has been reported for infant pertussis by investigators in other countries [12, 18–20, 27, 28, 30]. Infants with pertussis may also present with other atypical manifestations (i.e. not captured by the WHO case definition for pertussis) such as apnea and seizures [31], with the latter being associated with death in one recent series [32]. We did not have data on apnea, but 18% of the pertussis-positive infants in our series had seizures. Together, these data suggest that pertussis may be an important under-recognized cause of severe respiratory disease in young infants, and should not be excluded from the differential diagnosis based on the absence of classic clinical features. Furthermore, infant pertussis is likely to be substantially underreported in countries that conduct surveillance using the WHO clinical criteria.

To begin to address this problem in the US, the Council of State and Territorial Epidemiologists (CSTE) updated its pertussis surveillance case definition in 2014 to better capture disease in infants <1 year of age. The updated CSTE definition no longer requires a minimum duration of cough for reporting probable pertussis cases in this age group, and also added apnea to the list of associated clinical features that would satisfy the revised case definition in young infants [33]. Since we did not have data on the "typical" associated features of pertussis (paroxysmal cough, whoop, or post-tussive emesis) for the pertussis-positive infants with cough duration of <7 days, or data on apnea for any of the infants in the study, we cannot assess the performance of the new CSTE case definition in our sample. Importantly, the CSTE definition requires laboratory confirmation with culture for infants <1 year of age to be classified as confirmed cases. Therefore, even infants hospitalized with severe pertussis whose disease is confirmed with PCR, but who did not have a cough for ≥14 days, would only be classified as probable cases according to CSTE criteria.

Another notable finding from our study was that nearly half (45%) of the pertussis-positive infants had a documented fever within the first 24 hours of hospitalization. It is possible that the fever in the pertussis-positive infants in our study is attributable to concomitant or secondary bacterial or viral infections – for example, three of the five infants with fever had radiographic infiltrates (two meeting the WHO radiological criteria for pneumonia) and two had evidence of RSV infection by PCR. We did not have additional data on the course of fever to speculate on the potential etiologies of fever in these infants. However, the contribution of pertussis infection to their clinical presentation and the course of their illness should not be overlooked. Although fever is generally thought to be an uncommon manifestation of pertussis in this age group, especially compared to common viral pathogens, there is considerable variability in the prevalence of fever that has been reported in descriptive studies of infant pertussis. For example, in two recent community-based surveillance studies of infant pertussis in Pakistan and Zambia, no infants with PCR-confirmed pertussis had fever [34, 35]. In contrast, in other analyses of hospitalized infants who are found to have laboratory-confirmed pertussis, the prevalence of fever has been much higher – in one such study in South Africa it was nearly 25% [36], and in a study of pertussis-positive infants admitted to pediatric ICUs in the United Kingdom, 44% of infants had fever [19]. Finally, in a secondary analysis of data from a randomized controlled trial of maternal influenza immunization in South Africa – for which the surveillance definition for respiratory illness required the presence of fever – nearly a quarter (24.3%) of infants with laboratory-confirmed pertussis had fever [37]. Notably, in 2011 the Global Pertussis Initiative (GPI) proposed age-stratified clinical case definitions to account for the unique features of pertussis in younger children, stipulating the presence of "cough and coryza with no or minimal fever" in children 0–3 months of age [38]. While this definition improves upon the WHO clinical criteria for pertussis (which did not account for age), systematically excluding infants with fever from confirmatory laboratory testing for *B. pertussis* infection may lead to underestimation of the pertussis burden in young infants. This includes the important burden of pertussis co-infection with other respiratory pathogens, and the burden of pertussis in critically ill infants. Indeed, one recent study specifically identified fever as a predictor of more severe pertussis in children [39].

There are several limitations to our study. Since our sample was limited to hospitalized infants – who were therefore by definition severe cases – we cannot comment on the clinical characteristics of non-hospitalized (i.e. less severe) pertussis in this population, or on the background incidence of pertussis in Guatemala during the surveillance period. As a result, it is difficult to assess the potential impact of various control strategies, including routine maternal pertussis immunization, in our population. Similarly, our ARI case definition – which required either fever or an abnormal white blood cell count – may also bias toward the most severe pertussis cases. Since we obtained NP/OP swab specimens from only 90% of eligible infants (or 99% of enrolled infants), and of these only 93% were available for this analysis, it is possible that this introduced selection bias since the infants that did not undergo testing may be systematically different from those that did. However, we note that this rate of testing (93% of enrolled infants) is similar to the proportion of enrolled subjects for whom laboratory data were available in previously published analyses of other respiratory pathogens in this surveillance cohort (e.g. RSV [40] and human metapneumovirus [41]). The small number of cases in our study and the lack of data on the symptoms of early (i.e. coryza) or “typical” pertussis (i.e. paroxysmal cough, whoop, and post-tussive emesis) also limited our ability to identify characteristics that might be predictive of pertussis as a cause of ARI. Also, since apnea was not part of the clinical criteria used for enrollment, and this symptom is now recognized as a common manifestation of pertussis in young infants [31], we may have missed infants with pertussis that may differ from the infants included in our analysis. Ultimately, improved characterization of severe infant pertussis in diverse settings is essential to guide efforts to decrease morbidity and mortality in this vulnerable age group.

Some of the observed differences in the hospital course and clinical outcomes between the pertussis-positive and pertussis-negative infants may be due to unmeasured differences in their pre-hospital course – for example, the infants that tested positive for pertussis may have presented later in the course of their ARI compared to pertussis-negative infants, as evidenced by the longer duration of fever prior to presentation, which could partly explain the observed differences in clinical severity (e.g. higher case fatality rate). However, other than fever duration there were no significant differences in the types of symptom at the time of presentation between pertussis-positive and pertussis-negative infants, indicating that the differences in clinical outcomes were likely attributable to pertussis itself. Similarly, it is possible that some of the pertussis-positive infants in our study had an alternative diagnosis underlying their clinical presentation and *B. pertussis* was identified incidentally. However, the 11 pertussis-positive infants differed from the 290 pertussis-negative infants in several important parameters, including admission WBC, admission ALC, proportion requiring ICU admission, and case fatality rate, which is consistent with other reports of infants hospitalized with pertussis mono-infection [18, 42]. A systematic difference in these parameters between the pertussis-positive and pertussis-negative infants would not be expected if the assay were simply identifying asymptomatic carriage of the organism.

Conclusion

In this sample of infants hospitalized with ARI in Guatemala we found that pertussis-positive infants had high rates of complications, with higher mortality compared to pertussis-

negative infants. Furthermore, most of the pertussis-positive infants would not have been captured by the existing WHO clinical case definition, which suggests that the burden of pertussis in young infants is likely to be underestimated in developing countries such as Guatemala. Improvements in current case definitions would enhance pertussis surveillance and guide implementation of strategies to prevent severe disease in young infants.

Acknowledgments

This work was supported by the Emory Vaccinology Training Program [award number T32AI074492 from the National Institute of Allergy and Infectious Diseases to VKP]. The findings and conclusions in this report are those of the authors and does not necessarily represent the official position of the National Institute of Allergy and Infectious Diseases, the National Institutes of Health, or the Centers for Disease Control and Prevention.

References

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; 380(9859):2095–128. [PubMed: 23245604]
2. Vitek CR, Pascual FB, Baughman AL, Murphy TV. Increase in deaths from pertussis among young infants in the United States in the 1990s. Pediatr Infect Dis J. 2003; 22(7):628–34. [PubMed: 12867839]
3. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet. 2015; 385(9966):430–40. [PubMed: 25280870]
4. Centers for Disease C, Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women--Advisory Committee on Immunization Practices (ACIP), 2012. MMWR Morb Mortal Wkly Rep. 2013; 62(7):131–5. [PubMed: 23425962]
5. Public Health England. [Accessed December 18 2015] Questions and answers - Pertussis vaccination programme for pregnant women. Available at: http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1317136400742
6. Programa Nacional de Control de Enfermedades Inmunoprevenibles (Argentina). [Accessed December 18 2015] Resolución 2172/2013. Available at: http://www.msal.gob.ar/dinacei/index.php/institucional/marco-legal/424-resolucion-21722013
7. Ministerio de Salud. [Accessed December 18 2015] Esquema Nacional de Vacunación (El Salvador). Available at: http://www.salud.gob.sv/archivos/pdf/Esquema_Nacional_de_Vacunacion_2014.pdf
8. Ministerio de Salud. [Accessed December 18 2015] Esquema Nacional de Vacunación (Panama). Available at: http://www.minsa.gob.pa/sites/default/files/programas/esquema_de_vacunacion_revisado_marzo_2013.pdf
9. Sobanjo-Ter Meulen A, Duclos P, McIntyre P, et al. Assessing the Evidence for Maternal Pertussis Immunization: A Report From the Bill & Melinda Gates Foundation Symposium on Pertussis Infant Disease Burden in Low- and Lower-Middle-Income Countries. Clin Infect Dis. 2016; 63(suppl 4):S123–S33. [PubMed: 27838664]
10. Aquino-Andrade A, Martinez-Leyva G, Merida-Vieyra J, et al. Real-Time Polymerase Chain Reaction-Based Detection of Bordetella pertussis in Mexican Infants and Their Contacts: A 3-Year Multicenter Study. The Journal of pediatrics. 2017
11. Kowalzik F, Barbosa AP, Fernandes VR, et al. Prospective multinational study of pertussis infection in hospitalized infants and their household contacts. Pediatr Infect Dis J. 2007; 26(3): 238–42. [PubMed: 17484221]
12. Nieto Guevara J, Luciani K, Montesdeoca Melian A, Mateos Duran M, Estripeaut D. Hospital admissions due to whooping cough: experience of the del nino hospital in Panama. Period 2001–2008. Anales de pediatria. 2010; 72(3):172–8. Hospitalizaciones por Bordetella pertussis: experiencia del Hospital del Nino de Panama, periodo 2001–2008. [PubMed: 20153272]

13. Romanin V, Agustinho V, Califano G, et al. Epidemiological situation of pertussis and strategies to control it: Argentina, 2002–2011. Arch Argent Pediatr. 2014; 112(5):413–20. [PubMed: 25192521]
14. Mancaneira JF, Benedetti JR, Zhang L. Hospitalizations and deaths due to pertussis in children from 1996 to 2013. J Pediatr (Rio J). 2016; 92(1):40–5. [PubMed: 26235829]
15. Falleiros Arlant LH, de Colsa A, Flores D, Brea J, Avila Aguero ML, Hozbor DF. Pertussis in Latin America: epidemiology and control strategies. Expert review of anti-infective therapy. 2014; 12(10):1265–75. [PubMed: 25139010]
16. Ulloa-Gutierrez R, Avila-Aguero ML. Pertussis in Latin America: current situation and future vaccination challenges. Expert review of vaccines. 2008; 7(10):1569–80. [PubMed: 19053212]
17. Arlant LH, de Colsa A, Flores D, Brea J, Avila Aguero ML, Hozbor DF. Pertussis in Latin America: epidemiology and control strategies. Expert review of anti-infective therapy. 2014; 12(10):1265–75. [PubMed: 25139010]
18. Nieves DJ, Singh J, Ashouri N, McGuire T, Adler-Shohet FC, Arrieta AC. Clinical and laboratory features of pertussis in infants at the onset of a California epidemic. The Journal of pediatrics. 2011; 159(6):1044–6. [PubMed: 21925678]
19. Crowcroft NS, Booy R, Harrison T, et al. Severe and unrecognised: pertussis in UK infants. Archives of disease in childhood. 2003; 88(9):802–6. [PubMed: 12937105]
20. Berger JT, Carcillo JA, Shanley TP, et al. Critical pertussis illness in children: a multicenter prospective cohort study. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2013; 14(4): 356–65.
21. Verani JR, McCracken J, Arvelo W, et al. Surveillance for hospitalized acute respiratory infection in Guatemala. PloS one. 2013; 8(12):e83600. [PubMed: 24391792]
22. World Health Organization. Handbook IMCI Integrated Management of Childhood Illness. 2011. Available at: http://apps.who.int/iris/bitstream/10665/42939/1/9241546441.pdf
23. Tatti KM, Wu KH, Tondella ML, et al. Development and evaluation of dual-target real-time polymerase chain reaction assays to detect Bordetella spp. Diagn Microbiol Infect Dis. 2008; 61(3):264–72. Epub 2008/04/29. eng. [PubMed: 18440175]
24. Cherian T, Mulholland EK, Carlin JB, et al. Standardized interpretation of paediatric chest radiographs for the diagnosis of pneumonia in epidemiological studies. Bull World Health Organ. 2005; 83(5):353–9. [PubMed: 15976876]
25. Kusznierz G, Schmeling F, Cociglio R, et al. Epidemiologic and clinical characteristics of children with disease due to Bordetella pertussis in Santa Fe, Argentina. Revista chilena de infectologia : organo oficial de la Sociedad Chilena de Infectologia. 2014; 31(4):385–92. Caracteristicas clinicas y epidemiologicas de ninos con enfermedad por Bordetella pertussis en Santa Fe, Argentina. [PubMed: 25327190]
26. Namachivayam P, Shimizu K, Butt W. Pertussis: severe clinical presentation in pediatric intensive care and its relation to outcome. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2007; 8(3):207–11.
27. Farizo KM, Cochi SL, Zell ER, Brink EW, Wassilak SG, Patriarca PA. Epidemiological features of pertussis in the United States, 1980–1989. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 1992; 14(3):708–19. [PubMed: 1562663]
28. Halperin SA, Wang EE, Law B, et al. Epidemiological features of pertussis in hospitalized patients in Canada, 1991–1997: report of the Immunization Monitoring Program--Active (IMPACT). Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 1999; 28(6):1238–43. [PubMed: 10451159]
29. World Health Organization. Pertussis (whooping cough). Geneva, Switzerland: World Health Organization; 2003. WHO-recommended standards for surveillance of selected vaccine-preventable diseases; p. 28-30.
30. Bayhan GI, Tanir G, Nar-Otgun S, Aydin-Teke T, Metin-Timur O, Oz FN. The clinical characteristics and treatment of pertussis patients in a tertiary center over a four-year period. The Turkish journal of pediatrics. 2012; 54(6):596–604. [PubMed: 23692785]

31. Tanaka M, Vitek CR, Pascual FB, Bisgard KM, Tate JE, Murphy TV. Trends in pertussis among infants in the United States, 1980–1999. Jama. 2003; 290(22):2968–75. [PubMed: 14665658]
32. Winter K, Zipprich J, Harriman K, et al. Risk Factors Associated With Infant Deaths From Pertussis: A Case-Control Study. Clin Infect Dis. 2015; 61(7):1099–106. [PubMed: 26082502]
33. Davis, JP., DeBolt, C. [Accessed 10/30/2014 2014] Revision of the pertussis surveillance case definition to more accurately capture the burden of disease among infants <1 year of age. Available at: http://c.ymcdn.com/sites/www.cste.org/resource/resmgr/PS/13-ID-15.pdf
34. Omer SB, Kazi AM, Bednarczyk RA, et al. Epidemiology of Pertussis Among Young Pakistani Infants: A Community-Based Prospective Surveillance Study. Clin Infect Dis. 2016; 63(suppl 4):S148–S53. [PubMed: 27838667]
35. Gill CJ, Mwananyanda L, MacLeod W, et al. Incidence of Severe and Nonsevere Pertussis Among HIV-Exposed and -Unexposed Zambian Infants Through 14 Weeks of Age: Results From the Southern Africa Mother Infant Pertussis Study (SAMIPS), a Longitudinal Birth Cohort Study. Clin Infect Dis. 2016; 63(suppl 4):S154–S64. [PubMed: 27838668]
36. Soofie N, Nunes MC, Kgagudi P, et al. The Burden of Pertussis Hospitalization in HIV-Exposed and HIV-Unexposed South African Infants. Clin Infect Dis. 2016; 63(suppl 4):S165–S73. [PubMed: 27838669]
37. Nunes MC, Downs S, Jones S, van Niekerk N, Cutland CL, Madhi SA. Bordetella pertussis Infection in South African HIV-Infected and HIV-Uninfected Mother-Infant Dyads: A Longitudinal Cohort Study. Clin Infect Dis. 2016; 63(suppl 4):S174–S80. [PubMed: 27838670]
38. Cherry JD, Tan T, Wirsing von Konig CH, et al. Clinical definitions of pertussis: Summary of a Global Pertussis Initiative roundtable meeting, February 2011. Clin Infect Dis. 2012; 54(12):1756–64. Epub 2012/03/21. eng. [PubMed: 22431797]
39. Marshall H, Clarke M, Rasiah K, et al. Predictors of disease severity in children hospitalized for pertussis during an epidemic. Pediatr Infect Dis J. 2015; 34(4):339–45. [PubMed: 25260040]
40. McCracken JP, Prill MM, Arvelo W, et al. Respiratory syncytial virus infection in Guatemala, 2007–2012. J Infect Dis. 2013; 208(Suppl 3):S197–206. [PubMed: 24265479]
41. McCracken JP, Arvelo W, Ortiz J, et al. Comparative epidemiology of human metapneumovirus- and respiratory syncytial virus-associated hospitalizations in Guatemala. Influenza Other Respir Viruses. 2014; 8(4):414–21. [PubMed: 24761765]
42. Castagnini LA, Munoz FM. Clinical characteristics and outcomes of neonatal pertussis: a comparative study. The Journal of pediatrics. 2010; 156(3):498–500. [PubMed: 20056236]

Key points

In a surveillance study of hospitalized acute respiratory illness among young infants (age <2 months) in Guatemala, we identified 11 cases of laboratory-confirmed pertussis. Pertussis cases had a high rate of ICU admission, and higher case fatality rate than non-pertussis cases.

Table 1

Selected case definitions for pertussis

Definition, Year	Age	Clinical criteria: Cough duration	Clinical criteria: Associated features	Laboratory criteria (tests for *B. pertussis*)	Epidemiologic criteria	Interpretation
WHO, 2003 (27)	Any	≥14 days	Paroxysmal cough or Inspiratory whooping or Post-tussive vomiting	Positive culture or Positive PCR or Positive paired serology	None	**Clinically confirmed:** Meets clinical criteria only or Physician diagnosis of pertussis **Laboratory confirmed:** Meets clinical and laboratory criteria
CSTE, 2014 (31)	>1 year	≥14 days	Paroxysmal cough or Inspiratory whooping or Post-tussive vomiting	Positive culture or Positive PCR	Contact with a lab-confirmed case of pertussis	**Probable:** Meets clinical criteria **Confirmed:** Meets clinical criteria and positive PCR or Meets clinical and epidemiologic criteria or Positive culture with cough of any duration
	<1 year	Any	Paroxysmal cough or Inspiratory whooping or Post-tussive vomiting or Apnea (+/− cyanosis)			**Probable:** Same as for age >1 year or Meets clinical criteria for age <1 year and positive PCR or Meets clinical criteria for age <1 year and epidemiology criteria **Confirmed:** Same as for age >1 year

Abbreviations: WHO, World Health Organization; CSTE, Council of State and Territorial Epidemiologists; PCR, polymerase chain reaction

Table 2

Baseline data for infants aged <2 months tested for pertussis, Guatemala, 2007–2012

	Pertussis-positive (n=11)	Pertussis-negative (n=290)	p-value
Age in days, mean (range)	36.8 (22–52)	33.8 (1–60)	NS
Male sex	7 (63.6%)	149 (51.4%)	NS
Breastfed	10 (90.9%)	256 (88.6%)	NS
Preterm birth	3 (27.3%)	82 (28.4%)	NS
Residence			
Santa Rosa	7 (63.6%)	146 (50.3%	NS
Quetzaltenango	4 (36.4%)	144 (49.7%)	

Abbreviations: NS, non-significant (p>0.05)

Table 3

Outcomes and clinical characteristics of infants aged <2 months tested for pertussis, Guatemala, 2007–2012

	Pertussis-positive (n=11)	Pertussis-negative (n=290)	p-value
Outcomes			
Death	2 (18.2%)	10 (3.4%)	0.014
ICU admission	7 (63.6%)	102 (35.2%)	NS
ICU length of stay, days (range)	5.9 (2–15)	5.3 (1–24)	NS
Clinical characteristics			
Cough	10 (91%)	253 (87%)	NS
Cough duration prior to admission, days (range)	5.3 (1–15)	4.3 (1–30)	NS
Paroxysmal cough[a]	0 (0%)	14 (4.8%)	NS
Whoop[a]	1 (9.1%)	12 (4.1%)	NS
Post-tussive emesis[a]	0 (0%)	9 (3.1%)	NS
Fever (temperature ≥38°C)	5 (45.5%)	178 (61.4%)	NS
Cyanosis	1 (9.1%)	5 (1.7%)	NS
Pneumonia[b]	7 (63.6%)	252 (86.9%)	0.029
Seizure	2 (18.2%)	15 (5.2%)	NS
Laboratory characteristics			
Mean admission WBC per µl (range)	20900 (8900–36100)	12579 (3000–71900)	0.024
Mean admission ALC per µl (range)	11517 (3391–18880)	5591 (132–22792)	<0.001
Diagnosed with pertussis by a physician	3 (27.3%)	4 (1.4%)	<0.001

Abbreviations: ICU, intensive care unit; NS, non-significant (p>0.05); WBC, white blood cell count; ALC, absolute lymphocyte count

[a] Data only collected if cough duration exceeded 7 days

[b] Presumed pneumonia, defined according to the Integrated Management of Childhood Illness clinical criteria

Table 4

Clinical characteristics of hospitalized infants aged <2 months with laboratory-confirmed pertussis

Case	Age (days)	Sex	Duration of cough (days)	Temp (°C)[a]	Paroxysmal cough[b]	Whoop[b]	Post-tussive emesis[b]	Cyanosis	Pneumonia[c]	CXR findings	Seizure	Co-infections (RSV, influenza A or B)	WBC (cells/μl)	ALC (cells/μl)	Outcome
1	22	M	None	37.0	NA	NA	NA	N	Y	No infiltrate	N	N	21800	10377	Survived
2	23	F	1	38.0	NA	NA	NA	N	N	No infiltrate	N	N	23000	14260	Died
3	26	M	7	36.5	NA	NA	NA	N	Y	Other infiltrate[e]	Y	N	8900	3391	Survived
4	30	F	3	38.4	NA	NA	NA	N	Y	Consolidation[d]	N	N	36100	18880	Survived
5	34	M	15	38.0	N	N	N	N	Y	Other infiltrate[e]	N	Y(RSV)	10400	6552	Survived
6	35	M	1	37.0	NA	NA	NA	N	N	No CXR	N	N	NA	NA	Survived
7	40	M	5	37.0	NA	NA	NA	Y	N	Not interpreted	Y	N	18000	10422	Died
8	45	F	6	37.0	NA	NA	NA	N	N	Consolidation	N	N	26200	15222	Survived
9	46	M	3	37.0	NA	NA	NA	N	Y	No infiltrate[e]	N	N	19800	14098	Survived
10	52	M	9	38.0	N	Y	N	N	Y	Consolidation	N	Y(RSV)	33100	17675	Survived
11	52	F	3	38.0	NA	NA	NA	N	Y	No infiltrate	N	N	11700	4294	Survived

Abbreviations: CXR, chest X-ray; WBC, white blood count; ALC, absolute lymphocyte count; NA, not available

[a] Highest temperature within the first 24 hours of medical care

[b] Only those with a cough duration exceeding 7 days were asked about paroxysmal cough, whoop, or post-tussive emesis

[c] Presumed pneumonia, defined according to the Integrated Management of Childhood Illness clinical criteria for children aged 2 months to 5 years

[d] CXR obtained on hospital day 9

[e] Infiltrate interpreted by hospital radiologist and two clinicians, but not by study radiologists